# Primary Versus Specialty Care Outcomes for Depressed Outpatients Managed with Measurement-Based Care: Results from STAR*D

*Bradley N. Gaynes, MD, MPH[1], A. John Rush, MD[2], Madhukar H. Trivedi, MD[2], Stephen R. Wisniewski, PhD[3], G.K. Balasubramani, PhD[3], Patrick J. McGrath, MD[4,5], Michael E. Thase, MD[9], Michael Klinkman, MD[6], Andrew A. Nierenberg, MD[7], William R. Yates, MD[8], and Maurizio Fava, MD[7]*

[1]Department of Psychiatry University of North Carolina School of Medicine, Chapel Hill, NC, USA; [2]University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA; [3]Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, USA; [4]New York State Psychiatric Institute, New York, NY, USA; [5]College of Physicians and Surgeons, Columbia University, New York, NY, USA; [6]University of Michigan, Ann Arbor, MI, USA; [7]Massachusetts General Hospital, Boston, MA, USA; [8]University of Oklahoma College of Medicine, Tulsa, OK, USA; [9]University of Pennsylvania School of Medicine, Philadelphia, PA, USA.

***BACKGROUND:*** Whether the acute outcomes of major depressive disorder (MDD) treated in primary (PC) or specialty care (SC) settings are different is unknown.

***OBJECTIVE:*** To compare the treatment and outcomes for depressed outpatients treated in primary versus specialty settings with citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (www.star-d.org), a broadly inclusive effectiveness trial.

***DESIGN:*** Open clinical trial with citalopram for up to 14 weeks at 18 primary and 23 specialty sites. Participants received measurement-based care with 5 recommended treatment visits, manualized pharmacotherapy, ongoing support and guidance by a clinical research coordinator, the use of structured evaluation of depressive symptoms and side effects at each visit, and a centralized treatment monitoring and feedback system.

***PARTICIPANTS:*** A total of 2,876 previously established outpatients in primary ($n$=1091) or specialty ($n$=1785) with nonpsychotic depression who had at least 1 post-baseline measure.

***MEASUREMENTS AND MAIN RESULTS:*** Remission (Hamilton Depression Rating Scale for Depression [Hamilton] or 16-item Quick Inventory of Depressive Symptomatology-Self-Rated [QIDS-$SR_{16}$]); response (QIDS-$SR_{16}$); time to first remission (QIDS-$SR_{16}$). Remission rates by Hamilton (26.6% PC vs 28.0% SC, $p$=.40) and by QIDS-$SR_{16}$ (32.5% PC vs 33.1% SC, $p$=.78) and response rates by QIDS-$SR_{16}$ (45.7% PC vs 47.6% SC, $p$=.33) were not different. For those who reached remission or response at exit, the time to remission (6.2 weeks PC vs 6.9 weeks SC, $p$=.12) and to response (5.5 weeks PC vs 5.4 weeks SC, $p$=.97) did not differ by setting.

***CONCLUSIONS:*** Identical remission and response rates can be achieved in primary and specialty settings when identical care is provided.

*KEY WORDS:* primary care; depression; clinical trial; outcomes.
J Gen Intern Med 23(5):551–60
DOI: 10.1007/s11606-008-0522-3


*Trial registry name: Sequenced Treatment Alternatives to Relieve Depression (STAR*D)*
*Registration identification number: NCT00021528*
*URL for the registry: http://www.clinicaltrials.gov/ct/show/NCT00021528?order=2*
*Received August 20, 2007*
*Revised December 20, 2007*
*Accepted January 8, 2008*
*Published online February 5, 2008*

## INTRODUCTION

The outcomes of major depressive disorder (MDD) treated in primary (PC) or specialty care (SC) settings have never been directly compared. Conventional wisdom suggests that major depression presenting to primary care is a less severe[1–3] and less chronic illness.[1,4,5] However, more recent data suggest that newly treated depressions presenting to both settings are similar.[6] The only direct comparison concerning depressive illness in which patients presenting to both settings met identical eligibility criteria found that baseline patient characteristics, including depressive severity[7] and current psychiatric comorbidity,[8] were indistinguishable between settings.

Treatment guidelines suggest that patients with depression who present to primary care clinicians should be treated initially by them, unless suicidality or bipolarity is present, or 1 or 2 treatments have failed in the current episode.[9–11] These recommendations, based primarily on clinical consensus, imply that most patients with depression presenting to primary care have a similar likelihood of response as those seen in specialty settings.

These recommendations assume that adequate care is being provided in both specialty and primary care settings. However, the recently completed National Comorbidity Survey Replication reported that for patients identified as depressed and requiring treatment, only 41.9% (95% CI, 35.9–47.9) received adequate treatment (defined as 4 outpatient visits and 30 days of antidepressant therapy, or 8 psychotherapy sessions).[12] Of

those who receive depression treatment, 64% (95% CI 55.4–73.1%) of those seen in SC settings and 41% (95% CI 31.3–57.2%) of those seen in general medical settings received adequate care. Using a nationally representative sample of adults who were initiating a new episode of antidepressant treatment, Olfson and colleagues found that 42.4% discontinued their medication during the first month of treatment.[13]

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study was a broadly inclusive effectiveness trial that enrolled self-declared depressed outpatients from primary and specialty care settings using identical enrollment criteria. Our earlier analyses confirmed that depressive severity was not different, and symptomatic presentations did not differ substantially between the 2 settings at baseline.[7,8]. Whether representative patients who are treated with similar levels of adequate care have different outcomes in primary vs psychiatric care settings has never been directly evaluated. The data from STAR*D enabled us to determine whether the outcomes of patients who present with equivalent degrees of depression severity and are treated with equivalent high-quality measurement-based care differ by whether they presented to a primary or specialty setting.

This report addresses the following as""/because"" questions: (1) Did the treatment delivered in the 2 settings differ? (2) Did the symptomatic outcomes differ as a function of whether participants were treated in primary or specialty settings?

## METHODS

### Design Overview and Setting

The rationale and design of STAR*D are detailed elsewhere.[14–16] Briefly, the purpose was to define prospectively which of several treatments are most effective for outpatients with nonpsychotic depression who had an unsatisfactory clinical outcome to an initial and, if necessary, subsequent treatment(s). STAR*D participants were enrolled at 18 primary and 23 specialty (psychiatric) settings across the United States. Both primary and specialty care sites that provided care to public and private sector patients were selected on the basis of having (a) sufficient patient numbers, (b) sufficient numbers of clinicians, (c) sufficient administrative support, and (d) sufficient numbers of racial/ethnic minority subjects so that the study population could mirror the U.S. Census and results would be widely generalizable. The median number of clinicians at the 18 primary care sites was 14.5 compared to 12.0 at the 23 specialty sites. Three quarters of the facilities were privately owned, and approximately 2 thirds were freestanding (i.e., not hospital-based). Clinical Research Coordinators (CRCs) at each clinical site assisted participants and clinicians in protocol implementation and collection of clinical measures. A central pool of Research Outcome Assessors (ROAs) conducted telephone interviews (English or Spanish) to obtain primary outcomes.

### Participants

From July 2001 through April 2004, STAR*D enrolled 4041 participants 18–75 years of age who had a diagnosis of single or recurrent nonpsychotic depression. To enhance the generalizability of results, STAR*D enrolled only previously established outpatients seeking treatment in either primary or specialty settings and identified by their clinicians as having depression requiring treatment (confirmed by a DSM-IV checklist). Advertising for symptomatic volunteers was proscribed. Broadly inclusive selection criteria were used.[14,16] Patients with a baseline score ≥14 (moderate severity) on the CRC-rated 17-item Hamilton Rating Scale for Depression (Hamilton)[17,18] were eligible. This level of severity (a) indicates a clear need for treatment; (b) reflects a level of depression for which medication is superior to placebo[19,20]; (c) approximates the level of depressive severity seen in major depressive episodes in these settings[6,21]; and (d) is similar to the Hamilton eligibility criteria used in prior primary care clinical trials of major depression.[22–24] Patients who were pregnant, intending to become pregnant, or breastfeeding were excluded. Patients were excluded if they had a bipolar, psychotic, obsessive compulsive, or eating disorder; a substance abuse/dependence requiring inpatient treatment; a seizure disorder or other general medical condition that contraindicated medications used in the first 2 protocol treatment steps; or a clear history of nonresponse or intolerance (in the current major depressive episode) to any protocol treatment in the first 2 treatment steps. All other psychiatric and medical comorbidities were allowed.

Risks and benefits associated with STAR*D participation were explained to participants, who provided written informed consent before study entry. The protocol was approved and monitored by institutional review boards at the National Coordinating Center (Dallas), the Data Coordinating Center (Pittsburgh), each relevant Clinical Site and Regional Center, and the Data Safety and Monitoring Board of the National Institute of Mental Health (NIMH; Bethesda, MD, USA).

### Baseline Measures

At baseline, the CRCs collected standard demographic information, self-reported psychiatric history, and current medical conditions as evaluated by the Cumulative Illness Rating Scale (CIRS; a higher score indicates greater medical comorbidity).[25] The CRCs also assessed depressive symptom severity using the 16-item Quick Inventory of Depressive Symptomatology-Clinician-rated (QIDS-$C_{16}$). Participants completed the QIDS Self-Report (QIDS-$SR_{16}$)[26–28] (secondary outcomes).

Participants completed the Psychiatric Diagnostic Screening Questionnaire (PDSQ)[29,30] to estimate the presence/absence of 11 potential concurrent DSM-IV disorders. Based on prior reports,[29] we selected a scoring procedure and thresholds that yielded a 90% specificity in relation to the gold standard diagnosis rendered by a structured interview (the Structured Clinical Interview for DSM-IV, or SCID [31]).

ROAs, blinded to treatment characteristics and clinical site, used a structured telephone interview[32] at baseline to collect the Hamilton (primary outcome measure) and the 30-item Inventory of Depressive Symptomatology-Clinician-rated (IDS-$C_{30}$).[26,33] Responses to items on these measures were used to estimate the presence of atypical,[34] anxious,[35] and melancholic[36] symptom features.

An Interactive Voice Response system[37] collected health perceptions via the 12-Item Short Form Health Survey (SF-12)[38] and the Work and Social Adjustment Scale (WSAS).[39]

### Course of Treatment Measures

An integral part of our measurement-based care intervention (see below) was the collection at each visit of clinically relevant

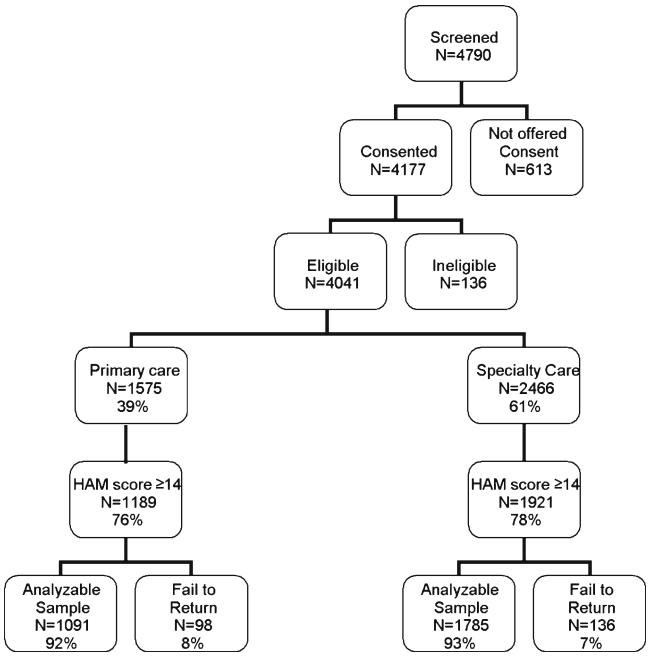



**Figure 1. Consort Chart Hamilton: 17-item Hamilton Rating Scale for Depression.**

information to inform medication decision making. At each visit, QIDS-$SR_{16}$ (primary outcome) and QIDS-$C_{16}$ ratings were obtained and participants reported side effects using three 7-point scales that evaluated frequency, intensity, and global burden measures, respectively.[14]

## Intervention

As detailed elsewhere,[40] citalopram was selected as a representative selective serotonin reuptake inhibitor given the relative absence of discontinuation symptoms, demonstrated safety in elderly and medically fragile patients, once-a-day dosing, few dose adjustment steps, and favorable drug–drug interaction profile.[14,16] The aim of the treatment was to achieve symptom remission (QIDS-$C_{16}$ score ≤5). The protocol[14,16] required a fully adequate dose for a sufficient time to maximize the likelihood of achieving remission and ensure that participants who did not reach remission were truly experiencing inadequate benefit from the medication. The treating clinician in each respective setting, whether primary or specialty care, made all antidepressant prescription decisions with guidance by the treatment protocol.

The protocol aimed to provide an optimal dose of citalopram based on dosing recommendations in a treatment manual (www.star-d.org). Citalopram was to be started at 20 mg/day and then raised to 40 mg/day by week 4 and to 60 mg/day (final dose) by day 42 (week 6). Appropriate flexibility was allowed (citalopram started at <20 mg/day, slower dose escalation) to minimize side effects; maximize safety; optimize the chances of therapeutic benefit; and enable patients with concomitant medical conditions, substance abuse/dependence, other psychiatric disorders, or sensitivity to medication side effects to be included safely in the sample.

The protocol recommended treatment visits at 2, 4, 6, 9, and 12 weeks (with an optional week 14 visit if needed). After an optimal trial (based on dose and duration), remitters and responders could enter the 12-month naturalistic follow-up; however, all non-remitters were encouraged to enter the subsequent randomized trial (Level 2 of STAR*D). Participants could discontinue citalopram before 12 weeks if: 1) intolerable side effects required a medication change, 2) an optimal dose increase was not possible owing to side effects or participant choice, or 3)

**Table 1. Baseline Characteristics by Clinical Setting**

| | Treatment Setting | | *p* value |
|---|---|---|---|
| | Primary Care | Specialty Care | |
| | *N*=1,091 (37.9%) | *N*=1,785 (62.1%) | |
| **Baseline Characteristics** | **%** | **%** | |
| Categorical measures | | | |
| Sociodemographic features | | | |
| Race | | | .02 |
| White | 73.8 | 77.0 | |
| African-American | 20.2 | 16.0 | |
| Other | 6.0 | 7.0 | |
| Hispanic | 19.1 | 9.2 | <.001 |
| Gender—Female | 70.1 | 59.8 | <.001 |
| Marital Status | | | <.001 |
| Never married | 24.7 | 31.1 | |
| Married | 42.6 | 41.2 | |
| Divorced | 27.9 | 25.7 | |
| Widowed | 4.8 | 2.0 | |
| Employment Status | | | .04 |
| Unemployed | 39.4 | 37.5 | |
| Employed | 53.8 | 57.6 | |
| Retired | 6.8 | 4.9 | |
| Education | | | <.001 |
| High School but < college | 80.2 | 71.4 | |
| ≥ College | 19.8 | 28.6 | |
| Insurance Status* | | | <.001 |
| Private | 47.9 | 53.0 | |
| Public | 22.8 | 9.0 | |
| None | 29.3 | 38.0 | |
| Clinical features | | | |
| History of attempted suicide | 14.1 | 20.3 | <.001 |
| Present Suicide Risk | 3.5 | 2.8 | .30 |
| Family History of Suicide | 3.5 | 3.6 | .88 |
| Family history of depression | 54.1 | 56.4 | .22 |
| Age at onset < 18 years | 33.3 | 40.5 | <.001 |
| Atypical features | 19.5 | 18.4 | .45 |
| Melancholic features | 21.2 | 24.9 | .02 |
| Anxious features | 58.2 | 50.1 | <.001 |
| Chronic depression | 29.9 | 22.4 | <.001 |
| Recurrent depression | 69.5 | 79.4 | <.001 |
| General medical comorbidities | | | |
| Musculoskeletal/integument | 28.3 | 13.8 | <.001 |
| Vascular | 23.3 | 12.6 | <.001 |
| Endocrine/breast/ metabolism | 20.7 | 10.3 | <.001 |
| Upper gastrointestinal | 14.8 | 9.1 | <.001 |
| Respiratory | 13.8 | 11.9 | .12 |
| Eyes, ears, nose, throat, larynx | 10.3 | 13.2 | .02 |
| Neurological | 10.1 | 4.9 | <.001 |
| Heart | 8.4 | 4.8 | <.001 |
| Genitourinary | 7.7 | 4.5 | <.001 |
| Liver | 6.6 | 2.0 | <.001 |
| Lower gastrointestinal | 6.5 | 3.6 | <.001 |
| Hematopoietic | 3.9 | 1.9 | <.002 |
| Renal | 2.1 | 0.8 | <.003 |

* Public Insurance includes both Medicare and Medicaid.

significant symptoms (QIDS-$C_{16}$ score ≥9) were present after 9 weeks at maximally tolerated doses. A web-based treatment monitoring system provided feedback to CRCs regarding individual participant fidelity to the treatment recommendations, enabling CRCs to guide physicians in vigorously dosing the medication when inadequate symptom reduction occurred despite acceptable side effects. These elements of the protocol represented an intensive effort to provide consistent, high-quality care.[41] The ultimate antidepressant dosing decision, however, was made by the treating clinician.

## Safety Assessments

In addition to side effects, serious adverse events were monitored with a multitiered approach that involved the CRCs, study clinicians, the interactive voice response system, the clinical manager, safety officers, regional center directors [42], and the NIMH Data Safety and Monitoring Board. Intolerance was defined a priori as either leaving treatment before 4 weeks for any reason, or leaving at or after 4 weeks because of intolerance.

## Concomitant Medications and Psychotherapy

Concomitant treatments for current medical conditions (as part of ongoing clinical care), for associated symptoms of depression (e.g., sleep, anxiety, and agitation), and for citalopram side effects (e.g., sexual dysfunction) were permitted based on clinical judgment. Stimulants, anticonvulsants, antipsychotics, alprazolam, nonprotocol antidepressants (except trazodone ≤200 mg at bedtime for insomnia) were prohibited. Also, concomitant evidence-based psychotherapies, such as cognitive-behavioral psychotherapy or interpersonal psychotherapy, were forbidden. Non evidence-based psychotherapy, such as supportive psychotherapy, was allowed.

## Outcomes

Our primary outcome was remission, defined as an exit Hamilton score ≤7 (or last observed QIDS-$SR_{16}$ score ≤5). As defined by the original proposal, participants for whom the exit Hamilton score was missing were designated as not achieving remission. Our secondary outcome was response, defined as a reduction of ≥50% in baseline QIDS-$SR_{16}$ at the last assessment.

**Table 2. Values of Continuous Measures**

| | Primary Care | Specialty Care | |
|---|---|---|---|
| Continuous measures | Mean (SD) | Mean (SD) | *p* value |
| Age (years) | 43.9 (13.0) | 38.9 (12.7) | <.001 |
| Years of schooling | 12.8 (3.4) | 13.8 (3.0) | <.001 |
| Income ($/month) | 2,352 (3,282) | 2,361 (2,872) | .02 |
| General Medical Comorbidities - CIRS Total Score | 5.3 (4.0) | 3.9 (3.5) | <.001 |
| SF-12: Physical | 46.0 (12.4) | 50.3 (11.6) | <.001 |
| SF-12: Mental | 27.6 (8.5) | 24.4 (7.7) | <.001 |
| WSAS | 23.7 (9.3) | 25.6 (8.3) | <.001 |
| HRSD17 (ROA) | 21.8 (5.2) | 21.8 (5.2) | .78 |

*CIRS Cumulative Illness Rating Scale, SF-12 12-item Short Form Health Survey, WSAS Work and Social Adjustment Scale, $HRSD_{17}$ 17-item Hamilton Rating Scale for Depression, ROA Research Outcome Assessor*

**Table 3. Treatment Characteristics in Relation to Symptomatic Outcome by Clinical Setting**

| | Primary Care | Specialty Care | *p* value |
|---|---|---|---|
| | *N*=1,091 | *N*=1,785 | |
| Treatment Characteristics | *n* (%) | *n* (%) | |
| Maximum dose of citalopram (mg/day) | | | <.001 |
| < 20 | 17 (1.6) | 46 (2.6) | |
| 20–39 | 290 (26.6) | 404 (22.7) | |
| 40–49 | 352 (32.4) | 510 (28.6) | |
| ≥ 50 | 429 (39.4) | 821 (46.1) | |
| Dose of citalopram at study exit (mg/day) | | | <.001 |
| < 20 | 29 (2.7) | 76 (4.3) | |
| 20–39 | 332 (30.5) | 452 (25.4) | |
| 40–49 | 348 (32.0) | 508 (28.5) | |
| ≥ 50 | 379 (34.8) | 745 (41.8) | |
| Time in treatment (weeks) | | | .56 |
| <4 | 127 (11.6) | 196 (11.0) | |
| ≥4 but <8 | 192 (17.6) | 293 (16.4) | |
| ≥8 | 772 (70.8) | 1,296 (72.6) | |

## Statistical Analysis

Summary statistics are presented as means and standard deviations for continuous variables, and percentages for discrete variables. Student's *t* tests and Mann–Whitney *U* tests were used to compare continuous baseline clinical and demographic features, treatment features, and side effect and serious adverse event rates across setting. Chi-square tests compared discrete characteristics across setting.

Logistic regression models were used to compare remission and response rates, after adjusting for the effect of baseline characteristics that were not equally distributed across setting and Regional Center. Times of first remission and first response were defined as the first observed point using clinic visit data. Log-rank tests were used to compare the cumulative proportion of participants with remission or response across settings. Kaplan–Meier curves were used to display cumulative proportion of first remission and first response by treatment setting. Additional exploratory logistic regression analyses were conducted to determine whether there was a differential effect of setting on remission based on the QIDS-$SR_{16}$ at exit by the baseline severity of depression.

Statistical significance was defined as a 2-sided *p* value less than 0.05. No adjustments were made for multiple comparisons, so results must be interpreted accordingly.

# RESULTS

## Sample Description/General

Most potential participants approached for the study were both eligible and enrolled (see Fig. 1). The study enrolled 4,041 eligible participants, 39% (*n*=1,575) from primary and 61% (*n*=2,466) from specialty care. The percentages of participants with a Hamilton <14 (15% PC and 15% SC), with a missing baseline Hamilton (9% PC vs 7% SC), and without a post-baseline measure (8% PC vs 7% SC) did not differ by setting. The evaluable sample of 2,876 consisted of 1,091 participants

**Table 4. Number of Visits**

| | Primary Care | Specialty Care | |
|---|---|---|---|
| | Mean (SD) | Mean (SD) | *p* value |
| Number of visits | 4.7 (1.5) | 4.9 (1.5) | .005 |
| Time to first treatment visit (weeks) | 2.4 (1.1) | 2.3 (1.1) | .10 |
| Time in treatment (weeks) | 10.1 (4.3) | 10.0 (4.1) | .46 |
| Time from final dose to study exit (weeks) | 5.3 (4.4) | 5.0 (3.7) | .09 |

in primary care and 1,785 participants in specialty care (38% and 62% of the final sample, respectively[40]).

## Sociodemographic and Clinical Features at Baseline

Primary care participants were older; were more likely to be female, have public insurance (Medicaid/Medicare), and African American; were substantially more likely to be Hispanic; and less likely to have completed college (Tables 1 and 2). Clinical features and course of depression were essentially indistinguishable between primary and specialty care participants. Presenting depressive severities were identical (Hamilton=21.8 in both PC and SC). The spectrum of depressive severity and the presence of current psychiatric comorbidities did not substantially differ between settings. Roughly half of the participants in each setting had an anxiety disorder.

Primary care participants were less likely to have recurrent depression (≥2 episodes) and to have their first episode before age 18, and slightly less likely to present with melancholic features. Fewer primary care participants reported a prior suicide attempt (14.1% vs 20.3%, $p<0.001$). Primary care participants were more likely to have a chronic depression (current episode ≥24months) and to present with anxious features.

Primary care participants had more current medical comorbidity. Of the 13 medical conditions identified (indicated by CIRS score ≥2, at least moderate disability), 11 were significantly more prevalent in primary care. Primary care participants had better mental health functioning and social adjustment scores, whereas specialty participants had better physical functioning and quality of life scores, although the magnitude of these differences was small.

## Treatment Characteristics by Clinical Setting

Treatment provided differed only minimally by setting (Tables 3 and 4). The number of actual visits was slightly lower in primary care (4.7 PC vs 4.9 SC, $p=.005$), but time to first treatment visit, time in treatment (mean of approximately 10 weeks), and time from final dose to study exit did not differ. Mean doses at Level 1 exit in primary settings (40.6 mg/day, SD=16.6) were slightly lower than those in specialty settings (42.5mg/day, SD=16.8, $p=.003$), although this is unlikely to be clinically meaningful. The variable most clearly distinguishing of the 2 settings was the greater tendency of psychiatric clinicians to prescribe higher doses of citalopram; smaller proportions of primary care participants received a dose of ≥50 mg during treatment (39.4%, vs 46.1%, $p<.001$) and were receiving ≥50 mg at study exit (34.8% vs 41.8%, $p<.001$). Still, in both settings, the most commonly prescribed dose range participants received at some point during the study, and at study exit, was ≥50 mg.

Despite the slightly higher prescribed doses of citalopram in specialty settings, we found no difference in side-effect burden (Table 5). Side effects, serious adverse events, and departure as a result of medication intolerance did not differ by setting.

## Symptomatic Outcomes by Clinical Setting: Remission and Response

Rates of remission were not significantly different between settings (Hamilton: 26.6% PC vs 28.0% SC, $p=.40$; QIDS-$SR_{16}$ [final visit]: 32.5% PC vs 33.1% SC, $p=.78$). These findings persist even after controlling for regional center and all baseline differences. Similarly, unadjusted response rates were not significantly different across settings (QIDS-$SR_{16}$: 45.7% PC vs 47.6% SC, $p=.33$). After adjusting, the response findings slightly favored primary care settings (odds ratio[OR]=0.79, $p=.04$; Table 6).

Mean depressive symptom severity at exit was virtually identical between settings (QIDS-$SR_{16}$: 9.2 PC vs 9.1 SC, $p=.63$), and the mean change in depressive severity did not differ by clinical setting (Table 7). Adjusting for baseline differences produced a slightly lower mean depressive severity at exit in

**Table 5. Adverse Events and Side Effects by Clinical Setting**

| | Primary Care | Specialty Care | |
|---|---|---|---|
| | *N*=1,091 | *N*=1,785 | |
| Adverse Events and Side Effects | *n* (%) | *n* (%) | *p* value |
| Maximum SE Frequency | | | .24 |
| None | 172 (15.9) | 276 (15.5) | |
| 10–25% of the time | 307 (28.3) | 501 (28.2) | |
| 50–75% of the time | 364 (33.6) | 550 (31.0) | |
| 90–100% of the time | 241 (22.2) | 450 (25.3) | |
| Maximum SE Intensity | | | .05 |
| None | 170 (15.7) | 272 (15.3) | |
| Trivial | 322 (29.7) | 471 (26.5) | |
| Moderate | 444 (41.0) | 729 (41.0) | |
| Severe | 148 (13.6) | 305 (17.2) | |
| Maximum SE Burden | | | .44 |
| No impairment | 215 (19.8) | 368 (20.7) | |
| Minimal-mild impairment | 445 (41.1) | 729 (41.0) | |
| Moderate-marked impairment | 342 (31.5) | 522 (29.4) | |
| Severe impairment-unable to function | 82 (7.6) | 158 (8.9) | |
| Serious Adverse Events | 40 (3.7) | 76 (4.3) | .43 |
| Death, nonsuicide | 1 | 2 | |
| Hospitalization for GMCs | 22 | 36 | |
| Medical illness without hospitalization | 2 | 2 | |
| Psychiatric hospitalization (substance abuse) | 2 | 6 | |
| Psychiatric hospitalization (suicidal ideation) | 11 | 25 | |
| Psychiatric hospitalization (worsening depression) | 2 | 4 | |
| Psychiatric hospitalization (other) | 0 | 2 | |
| Suicidal ideation(without hospitalization) | 2 | 4 | |
| Any Psychiatric SAE | 17 (1.6) | 40 (2.2) | .20 |
| Intolerance | 193 (17.7) | 297 (16.6) | .47 |

*GMC general medical condition, SE side effect, SAE serious adverse event*

Table 6. Remission, Response and Severity Status by Primary Care (PC) and Specialty Care (SC) Clinical Setting

| | Treatment Setting | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | PC | SC | Total | | | | | | |
| | *N*=1,091 | *N*=1,785 | *N*=2,876 | Unadjusted | | Adjusted* | | Adjusted† | |
| Outcome | % | % | % | OR | *p* | OR | *p* | OR | *p* |
| HRSD17 Remission | 26.6 | 28.0 | 27.5 | 1.08 | .40 | 0.86 | .15 | 0.85 | .19 |
| QIDS-SR16 Remission | 32.5 | 33.1 | 32.9 | 1.02 | .78 | 0.85 | .09 | 0.80 | .07 |
| QIDS-SR16 Response | 45.7 | 47.6 | 46.9 | 1.08 | .33 | 0.90 | .27 | 0.79 | .04 |

*Adjusted for Regional Center
† adjusted for Regional Center and age, years of education, ethnicity, gender, marital status, insurance status, level of education, age of onset, number of major depressive episodes, length of current episodes, CIRS total score, SF–12 physical, SF–12 mental, WSAS history of attempted suicide, melancholic depression, anxious depression, PDSQ items: OCD, panic, social phobia, drug abuse, hypochondriasis
*$HRSD_{17}$—17-item Hamilton Rating Scale for Depression, QIDS-$SR_{16}$ — 16-item Quick Inventory of Depressive Symptomatology - Self-Report, CIRS — Cumulative Illness Rating Scale, SF12–12–item short Form Health Survey, WSAS–Work and Social Adjustment Scale, PDSQ — Psychiatric Diagnostic Screening Questionnaire, OCD — Obsessive-Compulsive Disorder*

primary care settings, although the difference is unlikely to be clinically meaningful.

The time to the first indication of remission (Fig. 2) and response (data not shown) did not differ by setting (remission; $p$=.12, response; $p$=.97). For those who reached remission or response, the mean times to remission and response were 6.2 weeks primary vs 6.9 weeks specialty, and 5.5 weeks primary vs 5.4 weeks specialty, respectively. The percent remitting at each week did not differ by setting, with remission in each setting most likely to occur 6 weeks after the start of treatment.

## Association of Baseline Severity and Probability of Remission by Clinical Setting

As expected, baseline depressive severity had an effect on outcome. In both settings, higher baseline depressive severity was associated with a lower likelihood of remission (Hamilton: OR=0.76, $p$=.005 in PC; OR=0.80, $p$<.001 in SC for a five-unit increase in the Hamilton score) (QIDS-$SR_{16}$: OR=0.60, $p$<.001 in PC; OR=0.77, $p$=.004 in SC for a 5-unit increase in the QIDS-$SR_{16}$ score). Interestingly, after controlling for baseline and treatment differences, a differential effect ($p$=.006) on remission based on the QIDS-$SR_{16}$ was detected—results with Hamilton and QIDS-$SR_{16}$ were identical and we report only on the latter, for which a recorded outcome score was more likely (Fig. 3). Specifically, comparing remission rates in specialty vs primary care participants with baseline QIDS-$SR_{16}$ scores of 11.2, 16.2 (mean baseline score), and 21.2 gives the odds ratios of 0.626, 0.903, and 1.304, respectively. These higher odds ratios with higher baseline QIDS-$SR_{16}$ scores indicate that as the severity of depression increases, the odds of remission increase in specialty care relative to the odds of remission in primary care.

## DISCUSSION

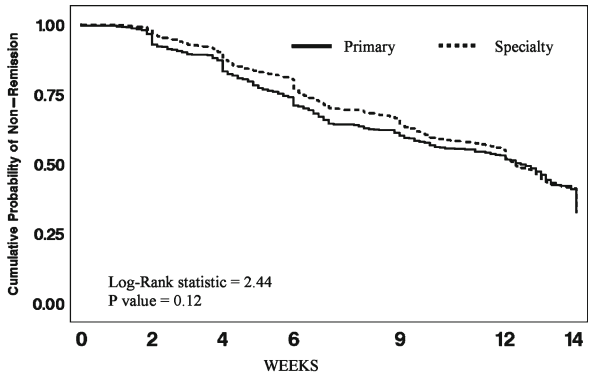
To our knowledge, this study is the first to directly compare symptomatic outcomes in a highly representative outpatient sample with nonpsychotic depression treated in primary vs specialty care settings. Given the broadly inclusive selection criteria, these results should apply to routine clinical practice in both settings if similar high-quality care procedures are implemented.

The scheduling of clinic visits was consistent with evidence-based treatment guidelines,[9,11,43] FDA recommendations,[44,45] and APA guidelines.[43] The mean dose of citalopram was higher than both the dose most commonly prescribed in clinical trials (20 mg per day)[46] and the average U.S. dose reported from a large managed care database (24 mg/day).[47] The mean dose at Level 1 exit did not differ between settings in a clinically

Table 7. Severity Status by Primary Care (PC) and Specialty Care (SC) Clinical Setting

| | Treatment Setting | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PC | SC | Total | | | | | | | |
| | *N*=1,091 | *N*=1,785 | *N*=2,876 | | Adjusted* | | | Adjusted† | | |
| | Mean (SD) | Mean (SD) | Mean (SD) | p | PC | SC | p | PC | SC | p |
| | | | | | Mean (SE) | Mean (SE) | | Mean (SE) | Mean (SE) | |
| Exit QIDS-SR16 | 9.2 (5.8) | 9.1 (5.9) | 9.1 (5.9) | .63 | 8.8(0.2) | 9.4 (0.15) | .04 | 9.8 (0.62) | 10.5 (0.61) | .03 |
| QIDS-SR16 % Change | −41.4 (35.2) | −43.6 (35.2) | −42.8 (35.2) | .17 | −43.3(1.19) | −42.4 (0.89) | .58 | −43.8 (3.95) | −40.4 (3.85) | .07 |

*Adjusted for Regional Center
† adjusted for Regional Center and age, years of education, ethnicity, gender, marital status, insurance status, level of education, age of onset, number of major depressive episodes, length of current episodes, CIRS total score, SF–12 physical, SF–12 mental, WSAS history of attempted suicide, melancholic depression, anxious depression, PDSQ items: OCD, panic, social phobia, drug abuse, hypochondriasis
*QIDS-$SR_{16}$ 16-item Quick Inventory of Depressive Symptomatology-Self-Report, CIRS–Cummulative Illness Rating Scale, SF12–12–item short Form Health Survey, WSAS–Work and Social Adjustment Scale, PDSQ–Psychiatric Diagnostic Screening Questionnaire, OCD–Obsessive–Compulsive Disorder*




| No. of patients | | | | | | | |
|---|---|---|---|---|---|---|---|
| Primary | 1087 | 1000 | 827 | 627 | 431 | 264 | 107 |
| Specialty | 1777 | 1684 | 1429 | 1165 | 795 | 457 | 168 |
| Total | 2864 | 2684 | 2256 | 1792 | 1226 | 721 | 275 |

**Figure 2. Time to Remission (QIDS-SR$_{16}$) by Clinical Setting. *QIDS-SR$_{16}$* 16-item Quick Inventory of Depressive Symptomatology-Self-Rated.**

meaningful way. The fact that vigorous, high-quality, measurement-based care was comparably delivered in self-declared real world patients in both settings suggests that dissemination of this strategy is feasible.

Our finding of similar depressive presentations across settings is contrary to conventional wisdom,[1–5] but supports results found in earlier studies.[6–8] Our findings suggest that clinicians would be well advised to prepare for patients with a similar range of depression severity and psychiatric comorbidity regardless of setting.

Overall, the likelihood of a clinically relevant benefit (i.e., remission, response) and the speed with which response or remission was reached did not differ across settings. This indicates that equivalent treatment provided across settings will likely produce generally equivalent outcomes.

Consistent with prior studies in both settings,[48–52] greater baseline depressive severity was associated with a lower likelihood of remission in each setting. The likelihood of improvement for participants with milder initial severity appeared greater in primary care. As initial depressive severity increased, the differences between the 2 settings decreased until, at approximately QIDS-SR$_{16}$ ≥16 (moderate-to-severe depression,[27] equivalent to Hamilton ≥20[28]), the likelihood of remission became greater in specialty care participants.

Why might clinical setting be an effect modifier? The effect cannot be explained by measured baseline demographics, psychiatric and medical comorbidities, or depression care provided, as our analysis controlled for these factors. Possible explanations involve patient and physician/clinic factors not measured in our study. For example, primary care clinicians may have been better able to manage comorbid medical conditions associated with milder depressive severity, leading to better psychiatric outcomes. Similarly, psychiatric clinicians may have been better able to manage associated comorbid psychiatric symptoms, substance use difficulties, or medication-related side effects. Indeed, psychiatric clinicians were more likely to concomitantly prescribe anxiolytics (11.7% vs 5.9%, $p<.001$), sedatives (16.1% vs 10.2%, $p<.001$), and trazodone (17.5% vs 11.9 %, $p<.001$), although they did not differ in the likelihood of prescribing Viagra (2.9% vs 3.9%, $p=0.17$). Also, participants at specialty sites likely had greater access to the non-depression-specific therapies (e.g., psychodynamic or supportive therapy) permitted by our protocol; however, we did not record such information.

What do these data mean for management of depression in real world primary and specialty care clinics? Patients with at least a moderate severity of depression improved in both settings, but primary care patients with more severe depressive symptoms might benefit from closer monitoring, and earlier consideration of referral or more vigorous dosing. These results highlight the import of using a chronic disease approach to enhance outcomes, consisting of a collaborative definition of problems, targeting and goal setting, and active and sustained follow-up with contact at specified intervals [53–58].

The main findings—that the 2 settings delivered a comparable level of high-quality depression care and equivalent outcomes—occurred within the context of a measurement-based care approach. This systematic approach to treatment is designed to be easily implemented in busy primary care or psychiatric practices.[59] The routine measurement of symptoms and side effects using easily administered tools, with guidance at critical decision points regarding when and how to modify the medication doses, provides a flexible treatment approach to ensure the delivery of an adequate dose and duration of the antidepressant medication(s) and makes it easier for clinicians to use a decision support system.[60] As with prior approaches, [22,61–66] the use of staff to closely monitor response and manage care in each setting is a key component of measurement-based care. However, measurement-based care further involves the use of critical decision points, which are scheduled times during treatment when the algorithm prompts clinicians to actively decide on a management change based on time on medication, total depressive severity score, and toleration of side effects. The algorithm applied in this study reflects depressive severity scores assessed by the depression specialist (QIDS-C$_{16}$); however, the QIDS-SR$_{16}$ can substitute [28], making use of this approach even easier. These key features—having support staff collect easily administered depressive severity and side effects measures at follow-up, providing this feedback to treating clinicians whose management plan is guided by a flexible medication algorithm—have proven feasible in other busy real world primary care settings.[67]

Study limitations include the absence of randomization to primary or specialty clinics, meaning unknown patient factors

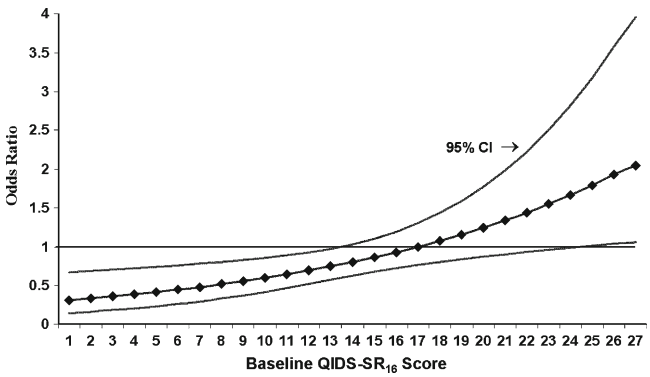



**Figure 3. Odds of remission in specialty care (vs Primary Care) as a function of baseline depressive severity. *QIDS-SR$_{16}$* 16-item Quick Inventory of Depressive Symptomatology-Self-rated. Odds ratios of <1 indicate a greater chance of remission in PC settings. Ratios >1 indicate a greater chance of remission in SC settings.**

might have affected outcomes. However, participants in the 2 settings were remarkably similar at presentation, and our analysis controlled for multiple potential confounders. Further, the distribution of depressive severity seen in this population is consistent with the spectrum reported by Kessler et al. in their recent nationally representative sample (10% mild, 38% moderate, 39% severe, 13% very severe),[12] and the racial/ethnic composition of the enrolled participants approximates U.S. Census (2000 U.S. Census), which both suggest that the sample was representative of depressed patients in the U.S. Finally, the participants' choosing of what clinic to attend mirrors what happens in routine clinical practice, which enhances the generalizability of our results.

## CONCLUSION

We have provided the first direct comparison of outcomes for patients presenting with identical severity of major depressive disorder in primary and specialty care settings that provide identical care. Our data suggest that identical remission and response rates can be achieved in both settings when identical care is provided. These data are the first to provide an evidence base on which to develop subsequent guidance for management in one or the other setting, and they underscore the importance of diligently managing depression in these settings.

***ACKNOWLEDGMENTS:*** *We would like to thank the STAR*D investigators for all the help in making this large and complex multicenter study possible and for generating the data for this report. We would also like to acknowledge the editorial support of Jon Kilner, MS, MA (Pittsburgh, Pennsylvania) and the secretarial support of Fast Word Information Processing Inc. (Dallas, Texas).*

*This project has been funded with Federal funds from the National Institute of Mental Health, National Institutes of Health, under Contract N01MH90003 to UT Southwestern Medical Center at Dallas (P.I.: A.J. Rush). Dr. Gaynes was supported in part by an NIMH K23 Career Development Award (MH01951-03). The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does the mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. The authors' work was independent of the funders (i.e., the funders had no involvement in the collection, analysis, and interpretation of data nor in the writing of this report or the decision to submit the article).*

***Conflict of Interest:*** *Bradley N. Gaynes, MD, MPH*
*Dr. Gaynes has received grants and research support from the National Institute of Mental Health; Agency for Healthcare Research and Quality; Robert Wood Johnson Foundation; the M—3 Corporation; Bristol-Myers Squibb Company; Novartis; Pfizer, Inc.; and Ovation Pharmaceuticals. He has performed as an advisor or consultant for Pfizer, Inc.; Shire Pharmaceuticals; and Wyeth-Ayerst. He has also received a speaker's honorarium from GlaxoSmithKline.*
*A. John Rush, MD*
*Dr. Rush has provided scientific consultation to or served on Advisory Boards for Advanced Neuromodulation Systems, Inc.; Best Practice Project Management, Inc.; Bristol-Myers Squibb Company; Cyberonics, Inc.; Forest Pharmaceuticals, Inc.; Gerson Lehman Group; GlaxoSmithKline; Jazz Pharmaceuticals; Eli Lilly & Company; Magellan Health Services; Merck & Co., Inc.; Neuronetics; Ono Pharmaceutical; Organon USA Inc.; Pamlab; Personality Disorder Research Corp.; Pfizer Inc.; The Urban Institute; and Wyeth-Ayerst Laboratories Inc. He has received royalties from Guilford Press and Health Technology Systems and research/grant support from the Robert Wood Johnson Foundation, the National Institute of Mental Health, the National Institutes of Health, and the Stanley Foundation; has been on speaker bureaus for Cyberonics, Inc., Forest Pharmaceuticals Inc., GlaxoSmithKline, and Eli Lilly & Company; and owns stock in Pfizer Inc.*
*Madhukar H. Trivedi, MD*
*Dr. Trivedi has received research support from Bristol-Myers Squibb Company; Cephalon, Inc.; Corcept Therapeutics, Inc.; Cyberonics, Inc.; Eli Lilly & Company; Forest Pharmaceuticals; GlaxoSmithKline; Janssen Pharmaceutica; Merck; National Institute of Mental Health; National Alliance for Research in Schizophrenia and Depression; Novartis; Pfizer Inc.; Pharmacia & Upjohn; Predix Pharmaceuticals; Solvay Pharmaceuticals, Inc.; and Wyeth-Ayerst Laboratories. He has served as an advisor or consultant for Abbott Laboratories, Inc.; Akzo (Organon Pharmaceuticals Inc.); Astra-Zeneca; Bayer; Bristol-Myers Squibb Company; Cephalon, Inc.; Cyberonics, Inc.; Fabre-Kramer Pharmaceuticals, Forest Pharmaceuticals; GlaxoSmithKline; Janssen Pharmaceutica Products, LP; Johnson & Johnson PRD; Eli Lilly & Company; Meade Johnson; Parke-Davis Pharmaceuticals, Inc.; Pfizer, Inc.; Pharmacia & Upjohn; Sepracor; Solvay Pharmaceuticals, Inc.; VantagePoint; and Wyeth-Ayerst Laboratories. He has received speaker honoraria from Abdi Brahim; Akzo (Organon Pharmaceuticals Inc.); Bristol-Myers Squibb Company; Cephalon, Inc.; Cyberonics, Inc.; Forest Pharmaceuticals; GlaxoSmithKline; Janssen Pharmaceutica Products, LP; Eli Lilly & Company; Pharmacia & Upjohn; Solvay Pharmaceuticals, Inc.; and Wyeth-Ayerst Laboratories.*
*Maurizio Fava, MD*
*Dr. Fava has received research support from Abbott Laboratories, Alkermes, Aspect Medical Systems, Astra-Zeneca, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithKline, J & J Pharmaceuticals, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, Novartis, Organon Inc., PamLab, LLC, Pfizer Inc, Pharmavite, Roche, Sanofi/Synthelabo, Solvay Pharmaceuticals, Inc., and Wyeth-Ayerst Laboratories. He has served on Advisory Boards and done Consulting for Aspect Medical Systems, Astra-Zeneca, Auspex Pharmaceuticals, Bayer AG, Best Practice Project Management, Inc., Biovail Pharmaceuticals, Inc., BrainCells, Inc. Bristol-Myers Squibb Company, Cephalon, Compellis, CNS Response, Cypress Pharmaceuticals, Dov Pharmaceuticals, Eli Lilly & Company, EPIX Pharmaceuticals, Fabre-Kramer Pharmaceuticals, Inc., Forest Pharmaceuticals Inc., GlaxoSmithKline, Grunenthal GmBH, Janssen Pharmaceutica, Jazz Pharmaceuticals, J & J Pharmaceuticals, Knoll Pharmaceutical Company, Lundbeck, MedAvante, Inc., Merck, Neuronetics, Novartis, Nutrition 21, Organon Inc., PamLab, LLC, Pfizer Inc, PharmaStar, Pharmavite, Precision Human Biolaboratory, Roche, Sanofi/Synthelabo, Sepracor, Solvay Pharmaceuticals, Inc., Somaxon, Somerset Pharmaceuticals, Takeda, TetraGenex Inc., Transcept Pharmaceuticals, and Wyeth-Ayerst Laboratories. Dr. Fava has served on the speaker's bureau for Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithKline, Novartis, Organon Inc., Pfizer Inc, PharmaStar, and Wyeth-Ayerst Laboratories. He has equity in Compellis and MedAvante.*
*Andrew A. Nierenberg, MD*
*Dr. Nierenberg has provided scientific consultation for BrainCells, Inc., Bristol-Myers Squibb, Eli Lilly & Company, Genaissance, GlaxoSmithKline, Innapharma, Janssen Pharmaceutica, Novartis, Pfizer, Sepracor, Shire, and Somerset, and has received research support from Bristol-Myers Squibb Company, Cederroth, Cyberonics, Inc., Forest Pharmaceuticals Inc., GlaxoSmithKline, Janssen Pharmaceutica, Lichtwer Pharma, Eli Lilly & Company, NARSAD, NIH, Pfizer Inc., the Stanley Foundation, and Wyeth-Ayerst. Dr. Nierenberg has received honoraria from Bristol-Myers Squibb, Cyberonics, Forest Pharmaceuticals, Eli Lilly & Company, GlaxoSmithKline, and Wyeth-Ayerst Laboratories.*
*Stephen R. Wisniewski, PhD*
*Dr. Wisniewski has received grants and research support from the National Institute of Mental Health. He has performed as a consultant for Cyberonics Inc., ImaRx Therapeutics, Inc., Bristol-Myers Squibb Company, Organon, and Case-Western University.*
*G.K. Balasubramani, PhD.*
*None disclosed.*
*Patrick J. McGrath, MD*
*Dr McGrath has received research support from the National Institute of Mental Health; National Institute on Alcohol Abuse and*

*Alcoholism; New York State Department of Mental Hygiene; Research Foundation for Mental Hygiene (New York State); GlaxoSmithKline; Eli Lilly; and Organon. He has been an advisor or consultant for GlaxoSmithKline, Lipha Pharmaceuticals, Novartis, and Somerset Pharmaceuticals.*
*Michael E. Thase, MD*
*Dr. Thase has provided scientific consultation to Astra-Zeneca, Bristol-Myers Squibb Company, Cephalon, Cyberonics, Inc., Eli Lilly & Company, Forest Pharmaceuticals, Inc., GlaxoSmithKline, Janssen Pharmaceutica, MedAvante, Inc., Neuronetics, Inc., Novartis, Organon, Inc., Sepracor Inc., Shire US Inc., Supernus Pharmaceuticals, and Wyeth-Ayerst Laboratories. Dr. Thase has been on the speakers' bureaus for AstraZeneca, Bristol-Myers Squibb Company, Cyberonics, Inc., Eli Lilly & Company, GlaxoSmithKline, Organon, Inc., Sanofi Aventis, and Wyeth-Ayerst Laboratories. Dr. Thase has equity holdings in MedAvante, Inc. and receives royalty income from American Psychiatric Publishing, Inc., Guilford Publications, and Herald House. He has provided expert testimony for Jones Day and Philips Lyttle, LLP.*
*Michael Klinkman, MD*
*Dr. Klinkman has received grants and research support from the National Institutes of Health (Roadmap initiative), the National Institute of Mental Health, Agency for Healthcare Research and Quality, Robert Wood Johnson Foundation, Lilly Foundation, and the Michigan BlueCross/Blue Shield Foundation. He has served on an advisory panel for Wyeth Pharmaceuticals.*
*William R. Yates, MD*
*Dr. Yates has received grants and research support from Eli Lilly and Company and Forest Laboratories. He has performed as an advisor or consultant for Eli Lilly and Company, Wyeth, Otsuko, and Forest Laboratories.*

***Corresponding Author:*** *Bradley N. Gaynes, MD, MPH, Department of Psychiatry University of North Carolina School of Medicine, CB #7160, Chapel Hill, NC 27599-7160, USA (e-mail: bngaynes@med.unc.edu).*

## REFERENCES

1. **Williamson PS, Yates WR.** The initial presentation of depression in family practice and psychiatric outpatients. Gen Hosp Psychiatry. 1989;113188–93. discussion 216–121.
2. **Schwenk T, Coyne J, Fechner-Bates S.** Differences between detected and undetected depressed patients in primary care and depressed psychiatric patients. Gen Hosp Psychiatry. 1996;18:407–15.
3. **Cooper-Patrick L, Crum RM, Ford DE.** Characteristics of patients with major depression who received care in general medical and specialty mental health settings. Med Care. 1994;32(1)15–24.
4. **Simon GE, VonKorff M.** Recognition, management, and outcomes of depression in primary care.[comment]. Arch Fam Med. 1995;4(2)99–105.
5. **Simon GE, Lin EH, Katon W, et al.**. Outcomes of "inadequate" antidepressant treatment.[comment]. J Gen Intern Med. 1995;10(12)663–70.
6. **Simon GE, Von Korff M, Rutter CM, Peterson DA.** Treatment process and outcomes for managed care patients receiving new antidepressant prescriptions from psychiatrists and primary care physicians. Arch Gen Psych. 2001;58(4)395–401.
7. **Gaynes BN, Rush AJ, Trivedi M, et al.**. A direct comparison of presenting characteristics of depressed outpatients from primary vs specialty care settings: preliminary findings from the STAR*D clinical trial. Gen Hosp Psychiatry. 2005;27(2)87–96.
8. **Gaynes BN, Rush AJ, Trivedi MH, et al.**. Major depression symptoms in primary care and psychiatric care settings: a cross-sectional analysis.. Ann Fam Med. 2007;5(2)126–34.
9. Depression guideline panel. Depression in primary care: Volume 2, Treatment of major depression. Vol AHCPR publication No. 93-0550. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1993.
10. Institute for Clinical Systems Improvement (ICSI). Major depression in adults in primary care. Vol May. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004.
11. National Institute for Clinical Excellence. Depression: management of depression in primary and secondary care. NICE. Available at: www.nice.org.uk/nicemedia/pdf/CG23quickrefguideamended.pdf. Accessed January 11, 2008.
12. **Kessler RC, Berglund P, Demler O, et al.**. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289(23)3095–105.
13. **Olfson M, Marcus SC, Tedeschi M, Wan GJ.** Continuity of antidepressant treatment for adults with depression in the United States. Am J Psychiatry. 2006;163(1)101–8.
14. **Rush A, Fava M, Wisniewski S, et al.**. Sequenced Treatment Alternatives to Relieve Depression (STAR*D): rationale and design. Control Clin Trials. 2004;25(1)119–42.
15. **Gaynes B, Davis L, Rush A, Trivedi M, Fava M, Wisniewski S.** The aims and design of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Prim Psychiatry. 2005;12236–41.
16. **Fava M, Rush A, Trivedi M, et al.**. Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. Psychiatr Clin North Am. 2003;26(2)457–94.
17. **Hamilton M.** A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–61.
18. **Hamilton M.** Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967;6:278–96.
19. **Paykel ES, Freeling P, Hollyman JA.** Are tricyclic antidepressants useful for mild depression? A placebo controlled trial. Pharmacopsychiatry. 1988;2(1)115–18.
20. **Paykel ES, Hollyman JA, Freeling P, Sedgwick P.** Predictors of therapeutic benefit from amitriptyline in mild depression: a general practice placebo-controlled trial. J Affect Dis. 1988;14(1)83–95.
21. **Coyne JC, Klinkman MS, Gallo SM, Schwenk TL.** Short-term outcomes of detected and undetected depressed primary care patients and depressed psychiatric patients. Gen Hosp Psychiatry. 1997;19(5)333–43.
22. **Hunkeler EM, Meresman JF, Hargreaves WA, et al.**. Efficacy of nurse telehealth care and peer support in augmenting treatment of depression in primary care [see comments] [comment]. Arch Fam Med. 2000;9(8)700–8.
23. **Katzelnick D, Simon G, Pearson S, et al.**. A randomized trial of a depression management program in high utilizers of medical care. Arch Fam Med. 2000;9:345–51.
24. **Schulberg HC, Madonia MJ, Block M, et al.**. Major depression in primary care practice. Clinical characteristics and treatment implications. Psychosomatics. 1995;36(2)129–37.
25. **Linn BS, Linn MW, Gurel L.** Cumulative illness rating scale. J Am Geriatr Soc. 1968;16(5)622–6.
26. **Trivedi MH, Rush AJ, Ibrahim HM, et al.**. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med. Jan 2004;34(1)73–82.
27. **Rush AJ, Trivedi MH, Ibrahim HM, et al.**. The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003;54(5)573–83.
28. **Rush AJ, Bernstein IH, Trivedi MH, et al.**. An evaluation of the Quick Inventory of Depressive Symptomatology and the Hamilton Rating Scale for Depression:a Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial report. Biol Psychiatry. 2006;59(6)493–501.
29. **Zimmerman M, Mattia JI.** A self-report scale to help make psychiatric diagnoses: the Psychiatric Diagnostic Screening Questionnaire. Arch Gen Psychiatry. Aug 2001;58(8)787–94.
30. **Zimmerman M, Mattia JI.** The Psychiatric Diagnostic Screening Questionnaire: development, reliability and validity. Compr Psychiatry42(3)175–189.
31. **First M, Spitzer , Gibbon M, Williams J.** Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington, D. C: American Psychiatric Press, Inc.; 1996.
32. **Simon GE, Revicki D, VonKorff M.** Telephone assessment of depression severity. J Psychiatr Res. 1993;27(3)247–52.
33. **Rush AJ, Gullion CM, Basco M, Jarrett RB, Trivedi MH.** The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med. 1996;26(3)477–86.
34. **Novick JS, Stewart JW, Wisniewski S, et al.**. Clinical and demographic features of atypical depression in outpatients with major depressive disorder: preliminary findings from STAR*D. J Clin Psychiatry. 2005;66(8)1002–11.
35. **Fava M, Alpert JE, Carmin CN, et al.**. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. Psychol Med. 2004;34(7)1299–308.
36. **Khan AY, Carrithers J, Preskorn SH, et al.**. Clinical and demographic factors associated with DSM-IV melancholic depression. Ann Clin Psychiatry. 2006;18(2)91–98.

37. **Kobak KA, Greist JH, Jefferson JW, Mundt JC, Katzelnick DJ.** Computerized assessment of depression and anxiety over the telephone using interactive voice response. MD Comput. 1999;16(3)64–8.
38. **Sugar CA, Sturm R, Lee TT, et al.**. Empirically defined health states for depression from the SF-12. Health Serv Res. 1998;33(4 Pt 1)911–28.
39. **Mundt JC, Marks IM, Shear MK, Greist JM.** The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry. 2002;180:461–4.
40. **Trivedi MH, Rush AJ, Wisniewski S, et al.**. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006;163 (1)28–40.
41. **Trivedi MH, Rush AJ, Wisniewski S, et al.**. Factors associated with health-related quality of life among outpatients with major depressive disorder: a STAR*D report. J Clin Psychiatry. 2006;67(2)185–95.
42. **Nierenberg AA, Trivedi MH, Ritz L, et al.**. Suicide risk management for the sequenced treatment alternatives to relieve depression study: applied NIMH guidelines. J Psychiatr Res. 2004;38(6)583–9.
43. American Psychiatric Association. Practice guideline for the treatment of patients with major depression (revision). Am J Psychiatry. 2000; 157 (suppl 4)1–45.
44. U.S. Food and Drug Administration. FDA Public Health Advisory: Suicidality in Adults Being Treated with Antidepressant Medications. Department of Health and Human Services [http://www.fda.gov/cder/drug/advisory/SSRI200507.htm]. Accessed January 11, 2008.
45. U.S. Food and Drug Administration. Antidepressant Use in Children, Adolescents, and Adults [http://www.fda.gov/cder/drug/antidepressants/default.htm]. Accessed January 11, 2008.
46. **Weilburg JB, O'Leary KM, Meigs JB, Hennen J, Stafford RS.** Evaluation of the adequacy of outpatient antidepressant treatment. Psychiatr Serv. 2003;54(9)1233–9.
47. **Sullivan PW, Valuck , Saseen J, MacFall HM.** A comparison of the direct costs and cost effectiveness of serotonin reuptake inhibitors and associated adverse drug reactions. CNS Drugs. 2004;18(13)911–32.
48. **Katon W, Schulberg H.** Epidemiology of depression in primary care. Gen Hosp Psychiatry. 1992;14(4)237–47.
49. **Katon W, Lin E, von Korff M, et al.**. The predictors of persistence of depression in primary care. J Affect Disord. 1994;3(12)81–90.
50. **Hirschfeld RM, Russell JM, Delgado PL, et al.**. Predictors of response to acute treatment of chronic and double depression with sertraline or imipramine. J Clin Psychiatry. Dec 1998;59(12)669–675.
51. **Ezquiaga E, Garcia A, Bravo F, Pallares T.** Factors associated with outcome in major depression: a 6-month prospective study. Soc Psychiatry Psychiatr Epidemiol. 1998;33(11)552–557. 1998/10//.
52. **Leary D, Costello F, Gormley N, Webb M.** Remission onset and relapse in depression: An 18-month prospective study of course for 100 first admission patients. J Affect Disord. 2000;57(1–3)159–71. /0 2000.
53. **Von Korff M, Gruman J, Schaefer J, Curry SJ, Wagner EH.** Collaborative management of chronic illness. Ann Intern Med. 1997;127(12)1097–1102.
54. **Von Korff M, Goldberg D.** Improving outcomes in depression. BMJ. 2001;323(7319)948–949. Oct 27.
55. **Katon W, Von Korff M, Lin E, Simon G.** Rethinking practitioner roles in chronic illness: the specialist, primary care physician, and the practice nurse. Gen Hosp Psychiatry. 2001;23(31)38–44.
56. **Wagner E, Grothaus L, Sandhu N, et al.**. Chronic care clinics for diabetes in primary care: a system-wide randomized trial. Diabetes Care. 2001;24(4)695–700.
57. **Wagner E, Austin B, Davis C, Hindmarsh M, Schaefer J, Bonomi A.** Improving chronic illness care: translating evidence into action. Health Aff (Millwood). 2001;20(6)64–78.
58. **Rothman AA, Wagner EH.** Chronic Illness Management: What Is the Role of Primary Care? Ann Intern Med. 2003;138(3)256–261. February 4, 2003.
59. **Trivedi MH, Rush AJ, Gaynes BN, et al.** Maximizing the Adequacy of Medication Treatment in Controlled Trials and Clinical Practice: STAR*D Measurement-Based Care. Neuropsychopharmacology. 2007/04/04/ online 2007.
60. **Kawamoto K, Houlihan CA, Balas EA, Lobach DF.** Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success.10.1136/bmj.38398.500764.8F. BMJ. April 2, 2005 2005;330(7494):765-.
61. **Katon W, Robinson P, Von Korff M, et al.**. A multifaceted intervention to improve treatment of depression in primary care. Arch Gen Psychiatry. 1996;53(10)924–32.
62. **Rost K, Nutting P, Smith J, Werner J, Duan N.** Improving depression outcomes in community primary care practice: a randomized trial of the quEST intervention. Quality enhancement by strategic teaming. J Gen Intern Med. 2001;16(31)43–49.
63. **Unutzer J, Katon W, Callahan CM, et al.**. collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. JAMA. 2002;288(22)2836–45.
64. **Bruce ML, Ten Have T, Reynolds CF III, et al.**. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. JAMA. 2004;291(9)1081–91.
65. **Dietrich AJ, Oxman TE, Williams JW J, et al.**. Re-engineering systems for the treatment of depression in primary care: cluster randomised controlled trial. BMJ. 2004;329(7466)602–5.
66. **Katon WJ, Von Korff M, Lin EHB, et al.**. The Pathways Study: a randomized trial of collaborative care in patients with diabetes and depression. Arch Gen Psychiatry. 2004;61(10)1042–9.
67. **Landis SE, Gaynes BN, Morrissey JP, Vinson N, Ellis A, Domino ME.** Generalist Care Managers for the Treatment of Depressed Medicaid Patients in North Carolina: A Pilot Study. BMC Family Practice. 2007;8 (1)7. Mar 5.